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Supplementary Materials for

Cooperative nature of viral replication

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This PDF file includes:

Figs. S1 to S7

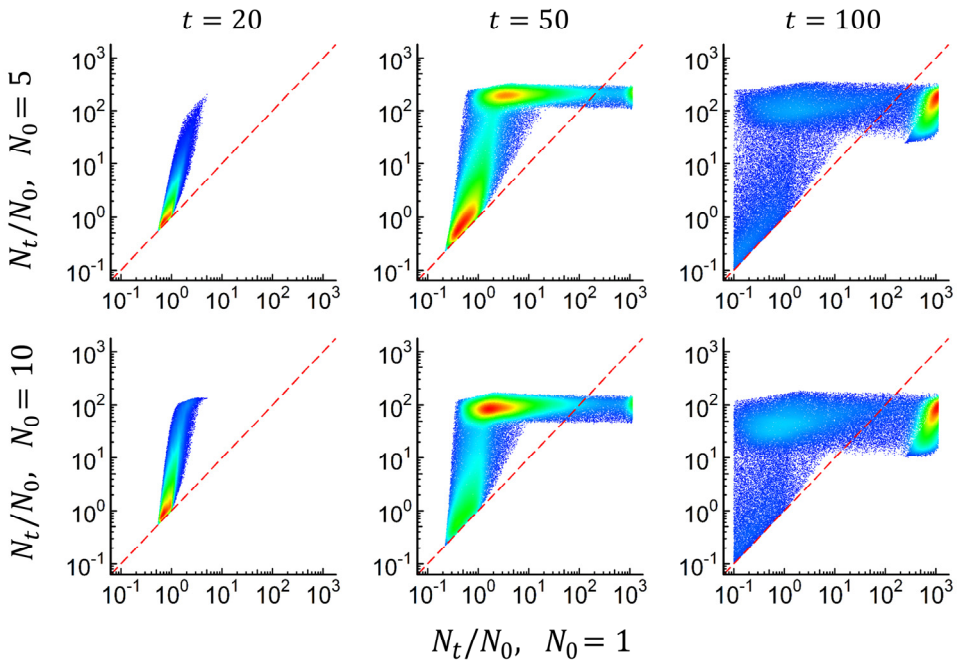

Fig. S1. Relationship between the number of founder genomes per cell and the per capita progeny production at different time points in the ODE model. Model details are indicated in Fig. 1. N_0: number of founder genomes per cell. N_t/N_0: per capita progeny production. Top: comparison between $N_0 = 1$ and $N_0 = 5$. Bottom: comparison between $N_0 = 1$ and $N_0 = 10$. Simulations were run using 100,000 different random sets of parameters within the indicated ranges: α (0-1), κ (0-$5 \cdot 10^{-4}$), γ (0-$5 \cdot 10^{-6}$), δ_g (0-$3 \cdot 10^{-2}$), δ_c (0-$3 \cdot 10^{-2}$), and δ_r (0-$3 \cdot 10^{-2}$). Each dot corresponds to a parameter set and data point density is indicated with colors. The red diagonal line indicates equal per capita progeny production for the two compared N_0 values. Values above this line indicate cooperativity.

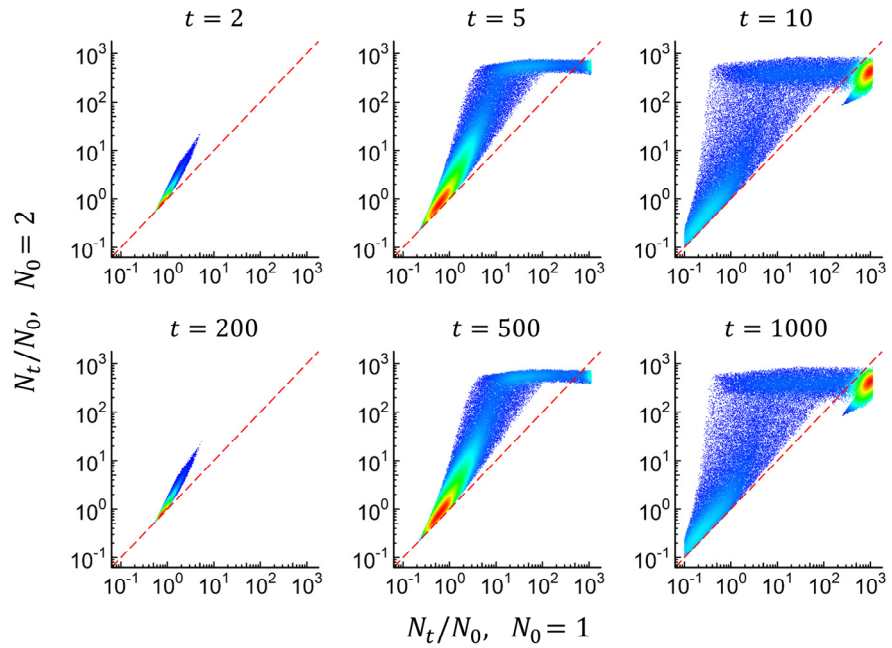

Fig. S2. Effect of parameter range on the relationship between the number of founder genomes per cell and the per capita progeny production in the ODE model. N_t/N_0 for $N_0 = 1$ versus $N_0 = 2$ using 100,000 random sets of parameters is shown for the indicated time points. Changes in the range of the tested parameter ranges only affect the speed of the infection cycle, and have no effect on cooperativity. Top: tenfold increase in parameter ranges with respect to Fig. 1E: α (0-10), κ (0-5·10^{-3}), γ (0-5·10^{-5}), δ_g (0-3·10^{-1}), δ_c (0-3·10^{-1}), and δ_r (0-3·10^{-1}). Bottom: tenfold reduction of parameter ranges in relation to Fig. 1E: α (0-0.1), κ (0-5·10^{-5}), γ (0-5·10^{-7}), δ_g (0-3·10^{-3}), δ_c (0-3·10^{-3}), and δ_r (0-3·10^{-3}). Each dot corresponds to a parameter set and data point density is indicated with colors. The red diagonal line indicates equal per capita progeny production for $N_0 = 1$ and $N_0 = 2$ values. Values above this line indicate cooperativity.

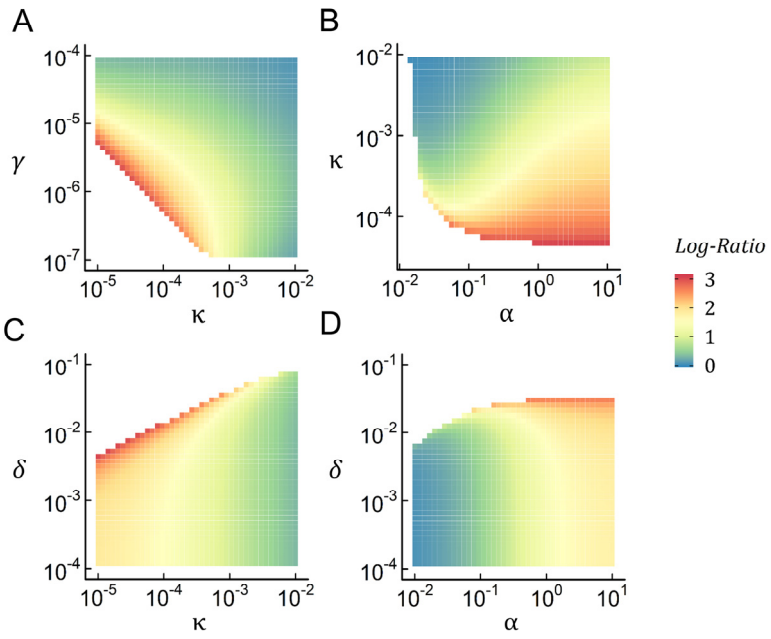

Fig. S3. Heat maps showing the effects of parameter values on cooperativity for the ODE model. We set out to compare the per capita progeny genome production (N_t/N_0) for a cell infected with a single founder genome ($N_0 = 1$) versus a cell coinfected with two founder genomes ($N_0 = 2$). The maximum log-ratio of these two quantities is shown. In all cases, this ratio was higher than 0, indicating cooperativity. Bluish areas indicate more similar per capita progeny production for $N_0 = 1$ and $N_0 = 2$ (less marked cooperativity), whereas reddish areas indicate higher per-capita progeny production for $N_0 = 2$ (greater cooperativity). Blank areas correspond to non-productive infections. Typically, replication became more cooperative as parameter combinations approached non-productive combinations, i.e. when replication was less efficient. Heat maps for κ-γ (A), κ-α (B), κ-δ (C) and α-δ (D) are shown, with $\delta = \delta_g = \delta_c = \delta_r$. κ and γ (which control viral resource production rate and the formation of replicative complexes, respectively) had a similar effect on cooperativity, such that γ-α and γ-δ combinations produced similar heat maps as κ-α and κ-δ combinations (not shown). For each heat map, the values for untested parameter were $\alpha = 5 \cdot 10^{-1}$ t^{-1}, $\kappa = 5 \cdot 10^{-4}$ units$^{-1} \cdot t^{-1}$, $\gamma = 10^{-6}$ units$^{-2} \cdot t^{-1}$, and $\delta = 10^{-2}$ t^{-1}).

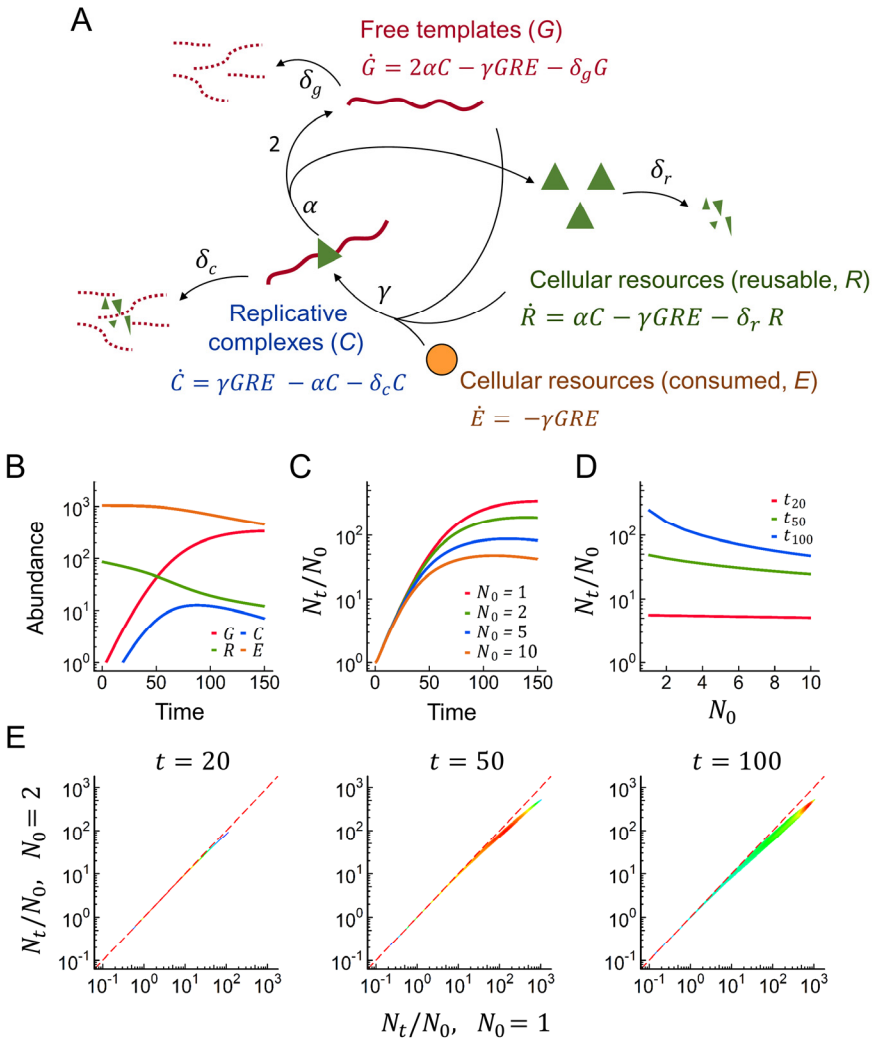

Fig. S4. Non-viral replication ODE model. A. Model definition. Replication complexes were formed at a rate γ from free templates and two types of cellular resources (reusable and consumed). These complexes dissociated at a rate α, producing a new copy of the replicon and releasing the template and reusable cellular resources. No replicon-encoded products were required for replication, as opposed to the viral model in Fig. 1**.** Free templates, complexes and reusable cellular resources were degraded at rates δ_g, δ_c, and δ_r, respectively. **B.** Dynamics of each variable, in arbitrary units for $\alpha = 5 \cdot 10^{-1}$ t^{-1}, $\gamma = 10^{-6}$ units^{-2}·t^{-1}, and $\delta_g = \delta_c = \delta_r = 10^{-2}$ t^{-1}. Simulations were started from $N_0 = G_0$ free viral genomes, using $C_0 = 0$, $R_0 = 86$, and $E_0 = 1047$ units. These parameter values were chosen such that the times of maximal growth rate for this model and the viral model in Fig. 1 were equal, ignoring degradation. **C.** Dynamics of per capita progeny production (N_t/N_0) for different N_0 values. **D.** Relationship between N_0 and N_t/N_0 at different time points. **E.** N_t/N_0 for $N_0 = 1$ versus $N_0 = 2$ at three time points for 100,000 random sets of parameters within the ranges α (0-1), γ (0-5·10^{-6}), δ_g (0-3·10^{-2}), δ_c (0-3·10^{-2}), and δ_r (0-3·10^{-2}). Each dot corresponds to a parameter set and data point density is indicated with colors. The red diagonal line indicates equal per capita progeny production for $N_0 = 1$ and $N_0 = 2$. Dots above this line would indicate cooperativity.

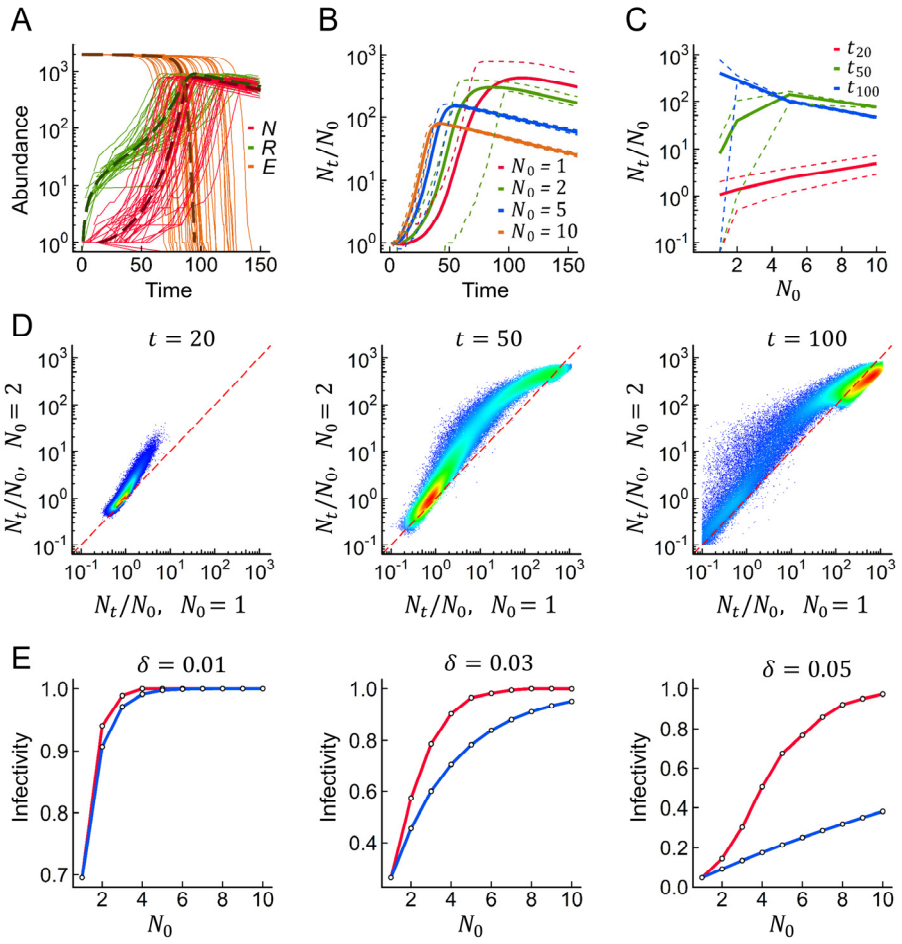

Fig. S5. Cooperative viral replication in a stochastic model. A. Dynamics of total genomes (N) and resources (R, E) for 50 replicate simulation ($\alpha = 5 \cdot 10^{-1}$ t^{-1}, $\kappa = 5 \cdot 10^{-4}$ units$^{-1} \cdot$t^{-1}, $\gamma = 10^{-6}$ units$^{-2} \cdot$t^{-1}, and $\delta_g = \delta_c = \delta_r = 10^{-2}$ t^{-1}). Dotted lines indicate the predictions from the ODE model. **B.** Dynamics of per capita progeny production (N_t/N_0) for different N_0 values. Solid lines indicate the average N_t/N_0 (1000 replicate simulations), whereas dotted lines show the 10th and 90th percentiles. For N_0 = 1, the 10th percentile corresponded to abortive viral replication (not shown). **C.** Relationship between N_0 and the average N_t/N_0 at different time points (solid lines: average from 1000 simulations; dotted lines: 10th and 90th percentiles). **D.** N_t/N_0 for N_0 = 1 versus N_0 = 2 at three time points for 100,000 random sets of parameters α, κ, γ, δ_g, δ_c and δ_r. Each dot corresponds to the average of 100 replicate simulations for a given parameter. Dot density is indicated with colors. Dots above the red line indicate cooperativity. **E.** Probability of non-abortive infection (infectivity) as a function of degradation rates ($\delta_g = \delta_c = \delta_r = \delta$). The red line shows the stochastic model output. The blue line shows infectivity under the independent action hypothesis, calculated as $P_{N_0} = 1-(1-P_1)^{N_0}$, where P_1 is the probability of productive infection for N_0= 1. The other model parameters were as shown in **A-C**.

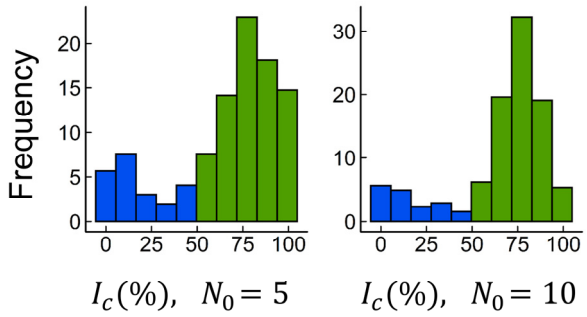

Fig. S6. Distribution of the fraction of I_c cells at equilibrium for N_0 = 5 and for N_0 = 10 in 1000 simulations using a stochastic intracellular model. Colored areas indicate simulations in which initial coinfection was beneficial (green) or detrimental (blue), excluding abortive infections. Initiating the infection with a single coinfected cell increased fitness in 77% and 87% of the simulations for N_0 = 5 and N_0 = 10, respectively (Binomial test: $P < 0.001$).

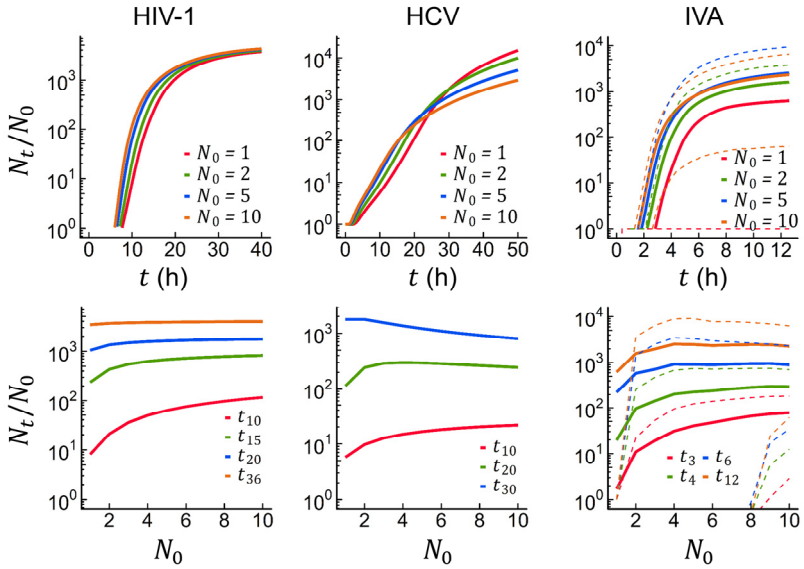

Fig. S7. Cooperative replication in previous models describing the infection cycles of HIV-1, HCV, and IVA. The per capita production of viral genomes, N_t/N_0, is shown for different time points and different N_0 values. For IVA, N_t was calculated as the number of copies of the least abundant segment. The HIV-1 and HCV models were based on a deterministic ODE system. For the stochastic IVA model the average V_t/V_0 obtained from 3000 replicate simulations is shown, including productive and abortive infections. Dashed lines indicate the 10th and 90th percentiles.